Zarxio™ (filgrastim)

Sandoz, a Novartis Company

Presentation to the Oncologic Drugs Advisory Committee

January 7, 2015

Introduction

Mark McCamish, MD, PhD
Global Head Biopharm. & Oncology Injectables Development
Sandoz

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Agenda

Introduction	**Mark McCamish, MD, PhD** Global Head Biopharm. & Oncology Injectables Development *Sandoz*
Analytical Demonstration of Biosimilarity	**Hansjoerg Toll, PhD** Head Analytical Characterization *Sandoz*
Biosimilar Clinical Development Program	**Sigrid Balser, PhD** Global Clinical Development *Sandoz*
A Clinical Perspective on Biosimilarity	**Louis Weiner, MD** Professor and Director of Lombardi Comprehensive Cancer Center *Georgetown University*
Totality of the Evidence and Concluding Remarks	**Mark McCamish, MD, PhD** Global Head Biopharm. & Oncology Injectables Development *Sandoz*

Additional External Consultants

- Kimberly Blackwell, MD
  - Professor of Medicine, Duke University Medical Center
- Paul Cornes, BM, BCh
  - Clinical Oncologist, Bristol Haemotology and Oncology Centre, UK
- Nadia Harbeck, MD
  - Professor of Medicine, University of Munich, Germany

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Evolution of the Concept of Sameness/Biosimilarity

- Generic small molecule drugs introduced **"sameness"** as a regulatory matter (1984)
  - **Complex generics**, e.g. Enoxaparin (2010) - FDA's 5 principles
- **Comparability** for manufacturing changes to currently approved drugs and biologics (FDA 1996), became ICH Q5E (2005)

  Comparable: A conclusion that products have highly similar quality attributes before and after manufacturing process changes …
- **Biosimilarity** (EU 2004, WHO 2009, US 2010) based on "highly similar" to the reference and no clinically meaningful differences

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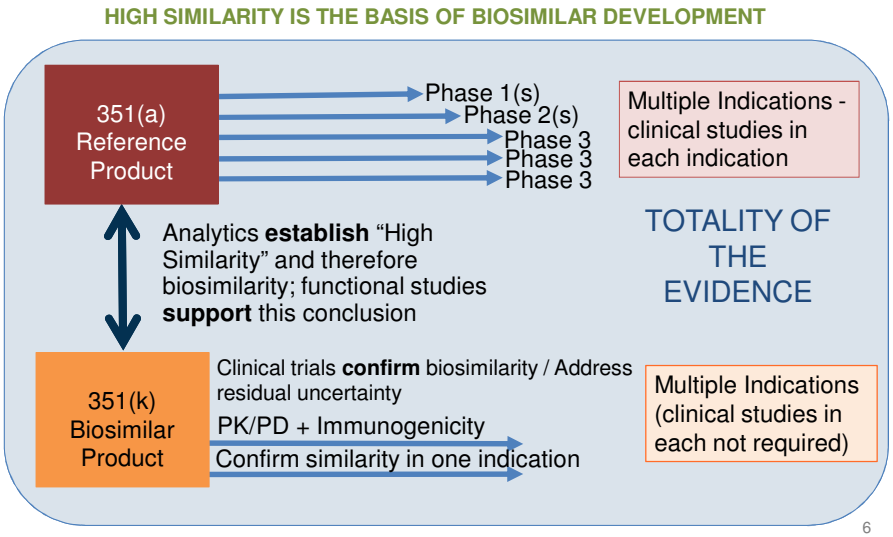
Biosimilar Development



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Overview of Zarxio (filgrastim)

- Zarxio is a biosimilar of the reference product Neupogen® (filgrastim)
  - Filgrastim (recombinant granulocyte-colony stimulating factor (G-CSF)), which stimulates the proliferation of white blood cells
- Was first approved in the EU in 2009[1] and subsequently developed for US marketing authorization
- Since approval, has become the volume leader in Europe

[1] Marketed as "Zarzio®" ex-US

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Zarxio Dose, Route of Administration, and Indications

- The BLA is for Zarxio pre-filled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL intended for subcutaneous and intravenous injection
- The proposed indications for Zarxio are identical to those of the reference product:
  - Cancer patients receiving myelosuppressive chemotherapy
  - Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
  - Cancer patients receiving bone marrow transplant
  - Patients undergoing peripheral blood progenitor cell collection and therapy
  - Patients with severe chronic neutropenia

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Zarxio US Development Program

- Analytical
  - Battery of structural and functional analyses
- Nonclinical
  - 5 animal studies to assess pharmacodynamics, toxicity, toxicokinetics, and local tolerance
- Clinical (confirming similarity)
  - 1 pivotal and 4 supportive PK/PD studies to demonstrate similar PK/PD
  - Comparative safety and efficacy clinical study to assess comparative efficacy

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Biosimilar Requirements and Zarxio Alignment

Statutory requirement	Statute language	Zarxio fulfillment of requirement
Reference product	*One reference product per application*	Single reference product (US-licensed Neupogen)
Analytical data	*Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components*	Analytical data demonstrate that Zarxio is highly similar to the reference product from a physiochemical and functional standpoint
Animal studies	*Animal studies (including the assessment of toxicity)*	Five animal studies assessed the pharmacodynamics, toxicity, toxicokinetics, and local tolerance of Zarxio compared to Neupogen and confirmed that the pharmacologic and toxicological profiles of the two products are similar

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Biosimilar Requirements and Zarxio Alignment

Statutory requirement	Statute language	Zarxio fulfillment of requirement
Clinical studies	*A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product*	Relevant clinical data were collected in 174 healthy volunteers, 388 breast cancer patients receiving myelosuppressive chemotherapy, and 121 healthy stem cell donors.
Mechanism of action	*The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product*	The mechanism of action of filgrastim as an rhG-CSF product is mediated by the selective binding to the G-CSF receptor and is similar across all indications. There are apparently no qualitative differences in the mechanism of action in neutropenia of different origins.

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Biosimilar Requirements and Zarxio Alignment

Statutory requirement	Statute language	Zarxio fulfillment of requirement
Conditions of use	*The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product*	Zarxio seeks licensure for the same indications for which the reference product is approved.
Route of administration, dosage form, and strength	*The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product*	Zarxio has the same route of administration, dosage form, and strengths as the reference product.

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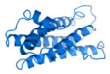
Analytical Demonstration of Similarity

Hansjoerg Toll, PhD
Head Analytical Characterization
Sandoz

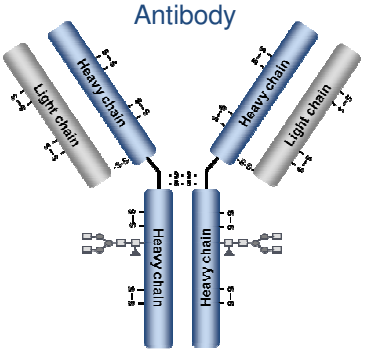
Filgrastim is a Relatively Simple Biologic

Filgrastim



- Protein only (non-glycosylated)
- Single main substance
- 1 chain
- 175 amino acids
- 18,799 Da

Antibody



- Glycoprotein
- Mixture of variants
- 4 chains
- 1330 amino acids
- 144,000 Da

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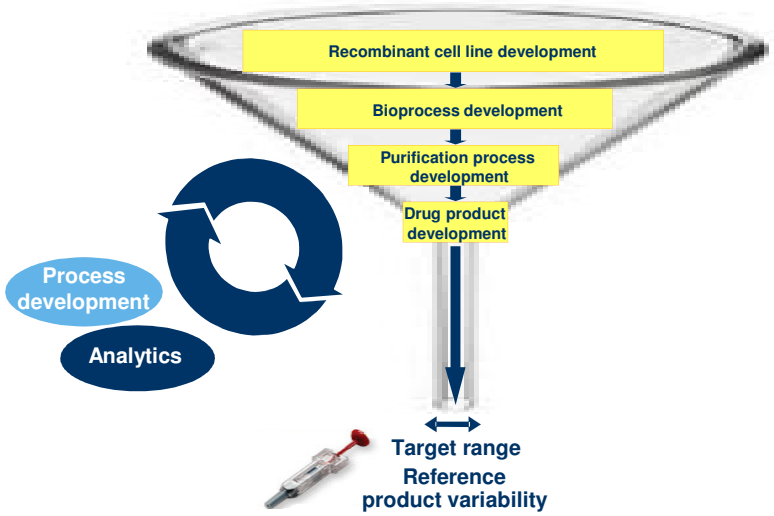
Source images: Sandoz

Biosimilars are Systematically Developed to Match the Reference Product



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Adapted from McCamish M & Woollett G. MAbs 2011; 3(2): 209–17

A Large Number of Zarxio and Neupogen Batches was Used for Assessing Similarity

Zarxio		Neupogen						
A00675111G	V200001	1009162	1025275	1020167	1024506	1029572	N0792AB	N1178AB
000657409G	V201002	1014928	1025872	1021955	1024772	1029837	N0839AA	N1179AB
000675011G	V201102	1020649	1026358	1024050	1025051	1029838	N0875AA	N1204AJ
030806	V201001	1021957	1026361	1000197	1025222	1032557	N0911AA	N1213AH
040906	V201101	1023892	1026689	1000539	1026494	1036993	N0996AD	
050906	V200201	1025269	1027991	1001143	1026519	1031133A	N0999AF	
111007		1027491	1031121	1003784	1026606	1032549A	N1005AA	
050409		1027493	1021952	1003865	1026690	N0512AA	N1014AB	
150210		1035682	1025277	1003937	1027142	N0527AA	N1062AA	
140210		1036971	1028687	1004154	1028082	N0577AA	N1113AG	
220810		1038184	1012002	1018725	1028497	N0586AA	N1114AA	
		P104490	1013453	1023368	1029228	N0715AF	N1114AJ	
		1022878	1017557	1023377	1029442	N0715AH	N1144AE	

Neupogen lots analyzed over a time frame of 10 years

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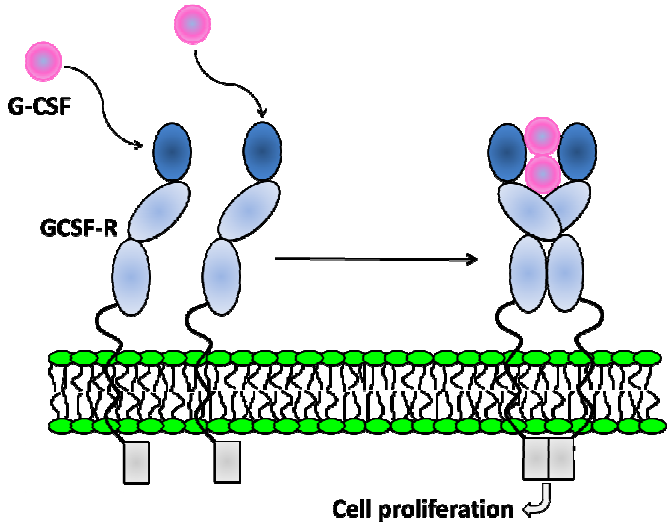
Source table: Sandoz

Filgrastim Exerts its Biological Activity by Receptor Activation



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Source images: Sandoz

What Matters for Filgrastim Safety and Efficacy

Quality Attribute	Criticality	Relevant for	Methods Used
Amino acid sequence	Very High	Efficacy, Safety, Immunogenicity	Edman, peptide mapping, MS
Potency	Very High	Efficacy, Safety	Bioassay
Target binding	Very High	Efficacy, Safety	Surface plasmon resonance
Protein concentration	Very High	Efficacy	Content determination
Higher order structure	High	Efficacy, Immunogenicity	CD and NMR spectroscopy
High-molecular weight variants/aggregates	High	Immunogenicity	Size exclusion chromatography
Oxidized variants	High	Efficacy	Reversed phase chromatography
Subvisible particles	High	Immunogenicity	Light obscuration
Truncated variants	Low	None	RP-HPLC-MS
Norleucine	Very Low	None	Reversed phase chromatography
Deamidation	Very Low	None	Cation exchange chromatography

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Today, Protein Analytics are Extremely Sensitive

Example: mass spectrometry

Year	Detection limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001

10 million-fold increase

Adapted from: Mire-Sluis, T.: The Regulatory Implications of the ever increasing power of Mass Spectrometry and its role in the Analysis of Biotechnology Products – Where do we draw the line? CASSS MassSpec 2012.

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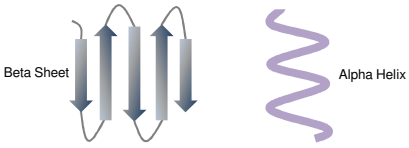
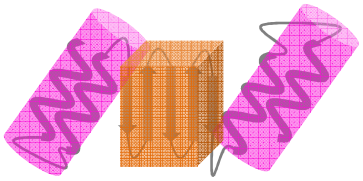
Amino Acid Sequence and Folding

Primary structure
is the amino acid sequence



Secondary structure
occurs when the sequence of amino acids are linked by hydrogen bonds



Tertiary structure
is the final folding which occurs when certain attractions are present between alpha helices and beta sheets

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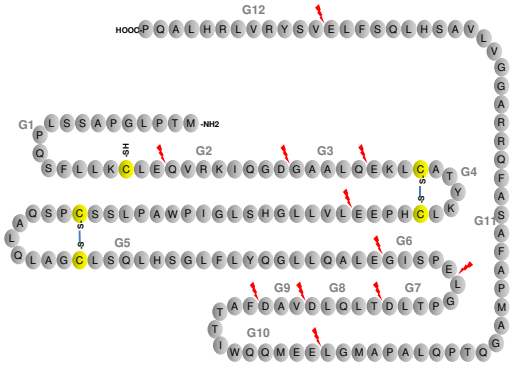
Source image: Sandoz

Amino Acid Sequence of Filgrastim is Determined by Several Methods



- Edman Sequencing
- Peptide Map
- Mass Spectrometry
- Amino Acid Analysis

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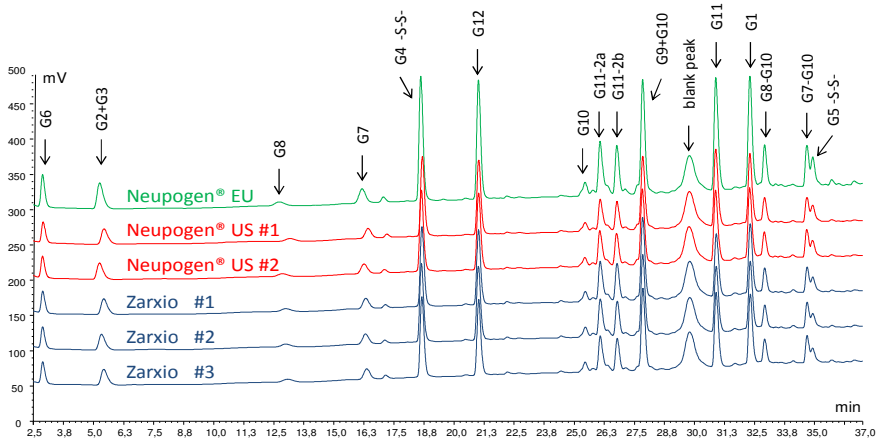
Source image: Sandoz

Peptide Map Confirms Identical Primary Structures of Zarxio and Neupogen



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Source graph: Sandoz

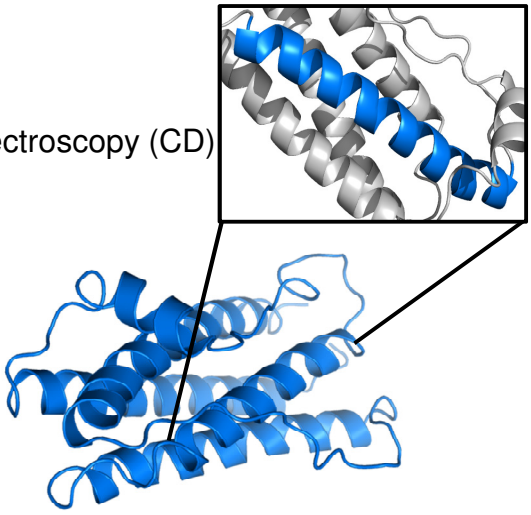
Folding of Filgrastim is Determined by Several Methods

Secondary structure

- Circular dichroism spectroscopy (CD)

Tertiary structure

- 1D NMR
- 2D NMR



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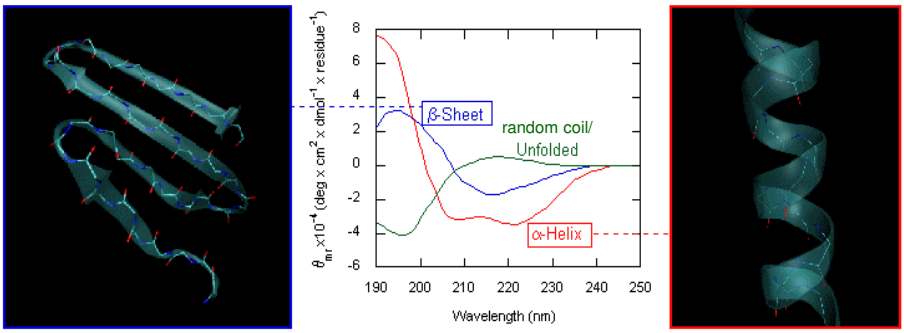
Source images: Sandoz

Circular Dichroism of Proteins

Left and right circularly polarized light is absorbed differently by secondary structural elements, e.g. α-helix, β-sheet and random coil/unfolded, CD is a tool to analyze the higher order structure



Figures kindly provided by Applied Photophysics Ltd.

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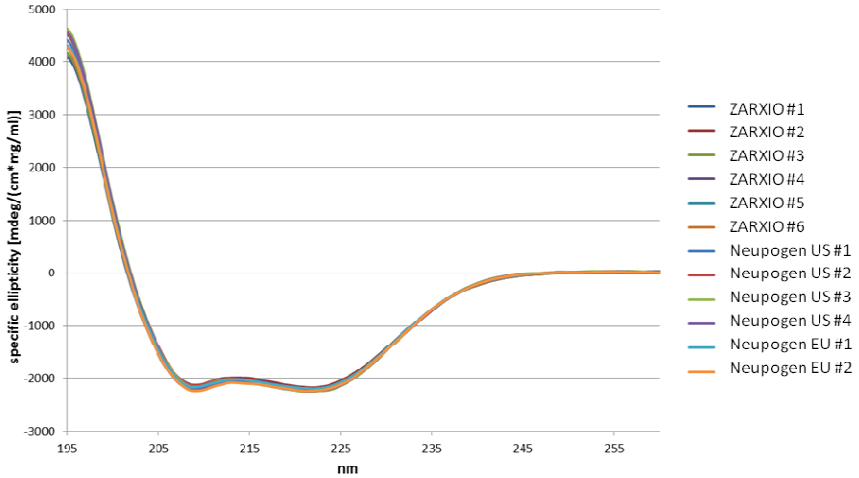
CD Confirms Highly Similar Secondary Structures of Zarxio and Neupogen



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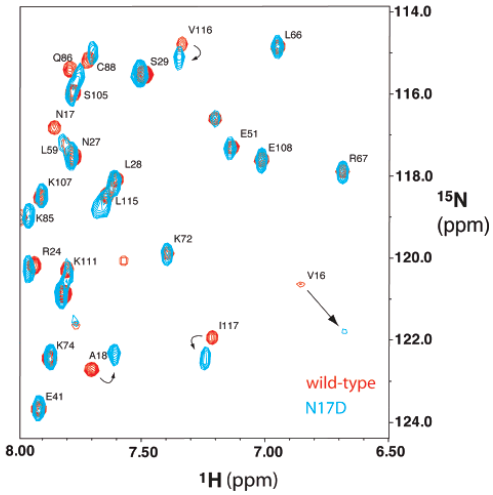
Source graph: Sandoz

2D NMR is Highly Sensitive in Detecting Differences in Structure



Single amino acid change can easily be detected

Example: Asn→ Asp (N17D) in GM-CSF

Yves Aubin, Christopher Jones, Darón I. Freedberg. Using NMR Spectroscopy to Obtain the Higher Order Structure of Biopharmaceutical Products. BioPharm International Supplements, Aug 2, 2010. Shown with kind permission of Dr. Aubin.

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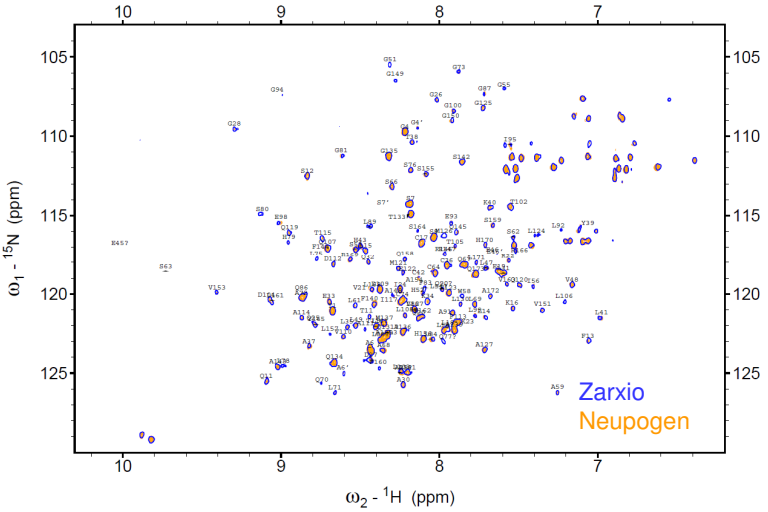
2D NMR Confirms Highly Similar Tertiary Structures of Zarxio and Neupogen



Source graph: Sandoz

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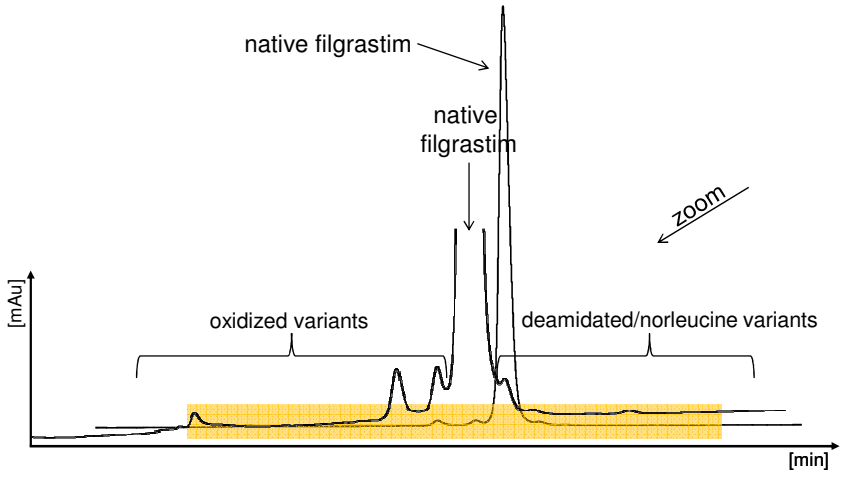
Highly Sensitive HPLC Detects Even Very Low Levels of Product Variants

RP-HPLC analytics can detect product-related variants with high sensitivity



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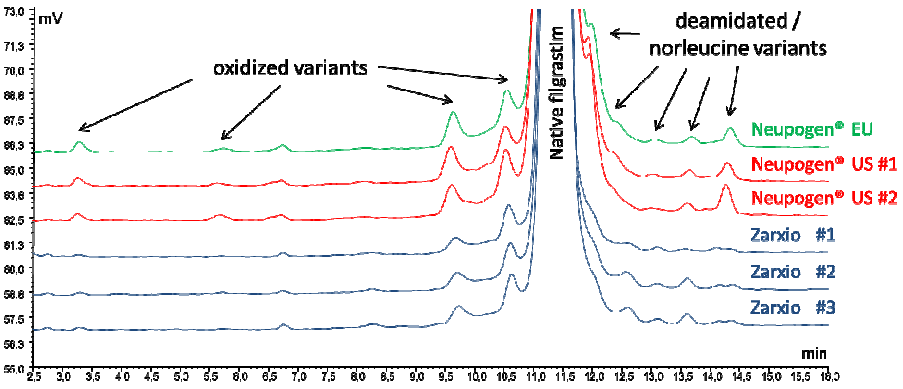
Source graph: Sandoz

Oxidized Variants and Purity are Highly Similar Between Zarxio and Neupogen

Reversed Phase HPLC



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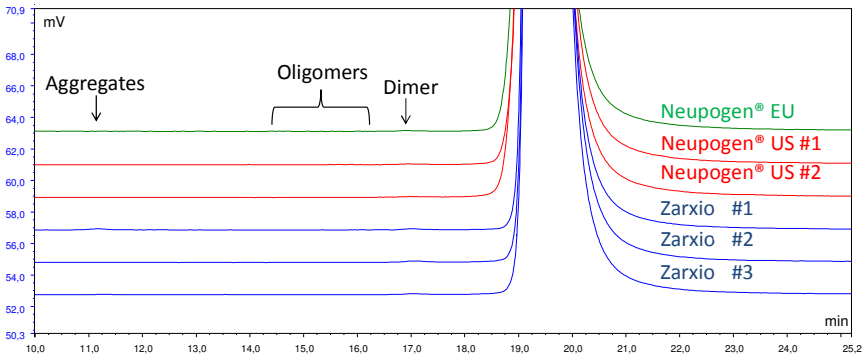
Source graph: Sandoz

Both Zarxio and Neupogen Have Very Low Aggregate Levels

Size Exclusion HPLC



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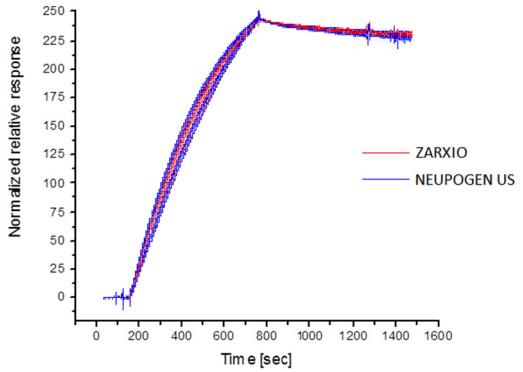
Source graph: Sandoz

Surface Plasmon Resonance Confirms Highly Similar Receptor Binding

Product	k_{on} [kM^{-1} s^{-1}]	k_{off} [μs^{-1}]	K_D [pM]
ZARXIO n=6	1.1	9.6	87.5
Neupogen US n=6	1.2	9.4	80.1



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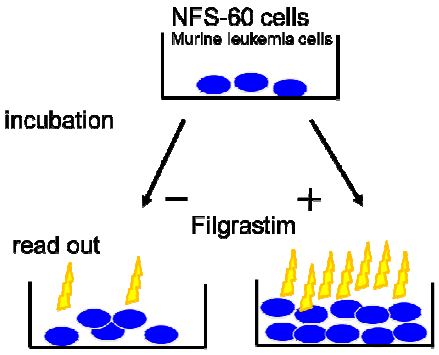
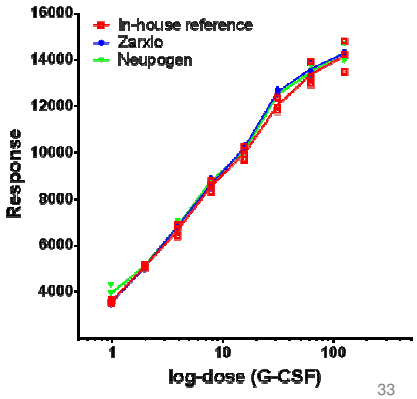
Source graph: Sandoz

Sensitive Biological Assay Confirms Highly Similar Biological Activity

Product	Zarxio	Neupogen US	Neupogen Product Information
Specific activity [U/mg x 10^8]	1.0 – 1.1	1.0 – 1.2	0.4 – 1.6





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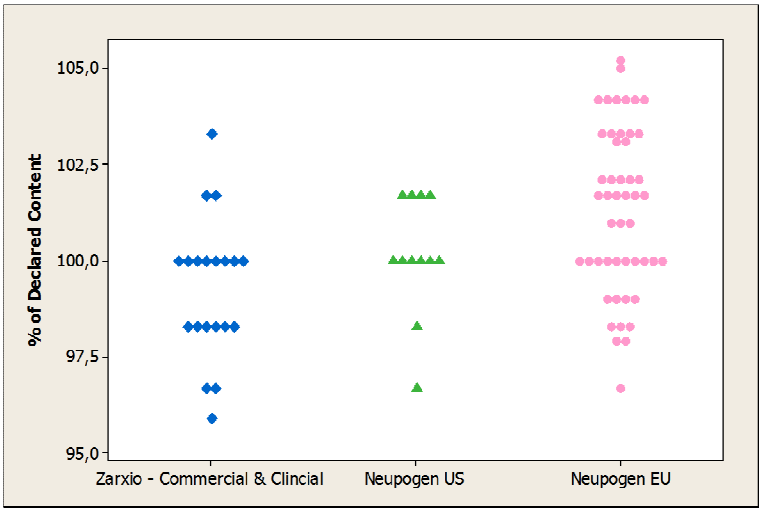
Source image: Sandoz

Zarxio Matches Neupogen in Content



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Source graph: Sandoz

Zarxio and Neupogen Formulations are Highly Similar

Function	Zarxio		Neupogen	
Active Ingredient	Filgrastim	0.600 mg/mL	Filgrastim	0.600 mg/mL
Other Ingredients				
Buffer	Glutamate pH 4.4	10 mM	Acetate pH 4.0	10 mM
Tonifying agent	Sorbitol	50 mg/mL	Sorbitol	50 mg/mL
Surfactant	Polysorbate 80	0.004%	Polysorbate 80	0.004%
Solvent	Water for Injection	ad 0.5 mL or 0.8 mL	Water for Injection	ad 0.5 mL or 0.8 mL

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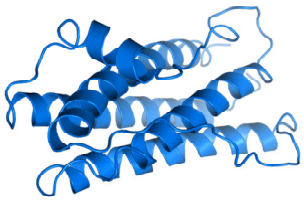
Zarxio and Neupogen are Highly Similar Regarding All Molecular Attributes

Structure
- Amino acid sequence
- Secondary structure
- Tertiary structure



Heterogeneity
- Product variants
  - Aggregated
  - Oxidized
  - Truncated
  - Deamidated
  - Norleucine
  - Minor variants

Process impurities

Function
- Receptor binding
- Biological activity

Pharmaceutical properties
- Concentration
- Particles
- Stability

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Biosimilar Clinical Development Program

Sigrid Balser, PhD
Global Clinical Development
Sandoz

Overview of Clinical Program

Study	Study population	N	Origin Neupogen	Dose	PK	PD	Efficacy	Safety	Immuno-genicity
109	Healthy volunteers	28	US	10 mcg/kg, s.c.	X	X		X	X
302	Breast cancer patients	218	US	5 mcg/kg, s.c.	X		X	X	X
101	Healthy volunteers	40	EU	10 mcg/kg, s.c.	X	X		X	X
102	Healthy volunteers	26	EU	5 mcg/kg, i.v.	X	X		X	X
103	Healthy volunteers	56	EU	2.5 mcg/kg, s.c. & 5 mcg/kg, s.c.	X	X		X	X
105	Healthy volunteers	24	EU	1 mcg/kg, s.c.	X	X		X	X
301	Breast cancer patients	170	Single-arm	300 mcg if < 60kg 480 mcg if ≥ 60kg			X	X	X
501	Healthy donors	240	Single-arm	10 mcg/kg, s.c.			X	X	

Plus extensive post-marketing pharmacovigilance data outside of the US

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Study 109

Pharmacokinetic and Pharmacodynamic Equivalence Established in Healthy Volunteers

Healthy Volunteers as a Sensitive Model to Establish Biosimilarity

- Healthy volunteers provide the most sensitive setting to confirm high similarity
  - Same clinically relevant markers (ANC and $CD34^+$ cells) and mode of action as in patient populations
  - Bone marrow is fully responsive to evaluate PD response
  - No confounding factors
  - Cross-over design reduces variability
  - Fully immunocompetent to assess immunogenicity

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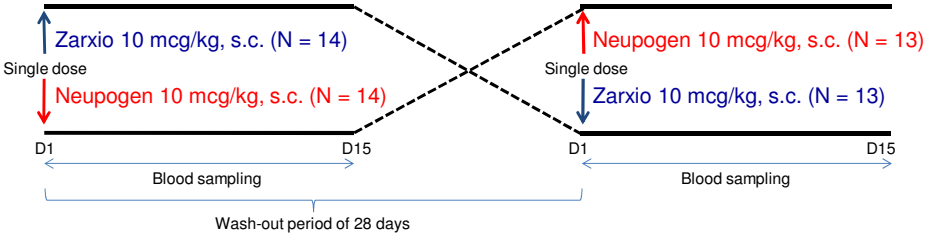
Study 109 – Design



Primary objectives (hierarchical test):	Secondary objectives:
• PD equivalence*: E_{max}, $AUEC_{0\text{-}120h}$ of absolute neutrophil count (ANC) • PK equivalence*: C_{max}, AUC_{last}	• $CD34^+$ cell count • Safety, immunogenicity and local tolerance

*Equivalence was assessed according to FDA endorsed bioequivalence margins of 80-125%

➢ Design was pre-discussed with FDA

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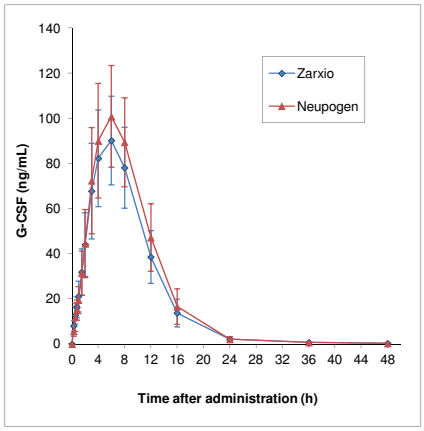
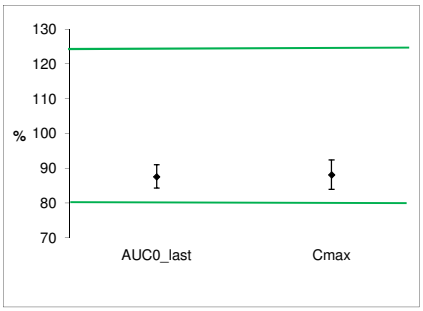
Study 109 – PK Results (Primary Endpoint)
Demonstrated PK Equivalence

Arithmetic mean ± SD - time profiles



Equivalence assessment with respect to FDA equivalence margins



Parameter	$AUC_{0\text{-last}}$	C_{max}
Ratio [%] Zarxio/Neupogen	87.65	88.13
90% CI [%]	84.39 – 91.04	84.00 – 92.46

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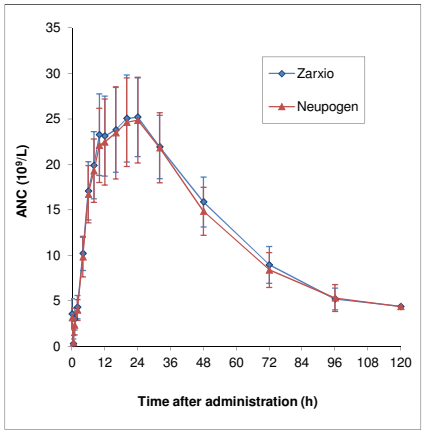
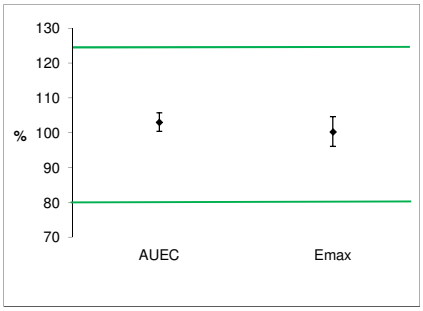
Study 109 – PD Results (Primary Endpoint)
Demonstrated PD Equivalence for ANC Response

Arithmetic mean ± SD - time profiles



Equivalence assessment with respect to FDA equivalence margins

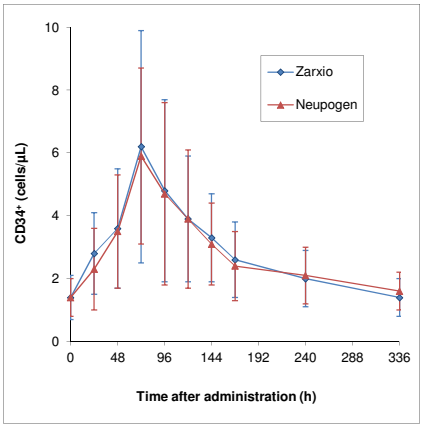


Parameter	$AUEC_{0\text{-}120h}$	E_{max}
Ratio [%] Zarxio/Neupogen	103.07	100.33
95% CI [%]	100.42 – 105.78	96.13 – 104.70

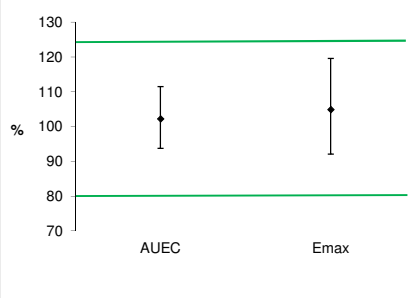
44

Study 109 – PD Results (Secondary Endpoint)
Demonstrated High PD Similarity for CD34+ Response

Arithmetic mean ± SD - time profiles



Similarity assessment with respect to FDA equivalence margins



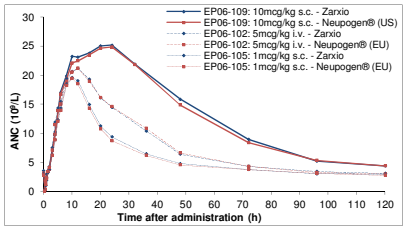
Parameter	$AUEC_{0-336h}$	E_{max}
Ratio [%] Zarxio/Neupogen	102.29	104.96
95% CI [%]	93.80 – 111.55	92.11 – 119.64

45

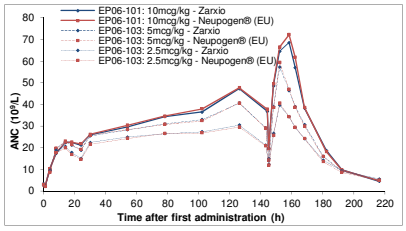
Overall Highly Similar ANC and CD34+ Responses

ANC profiles in Healthy Volunteers

Single-dose studies

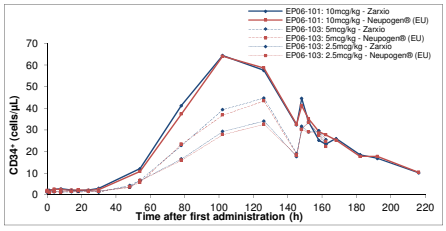


Multiple-dose studies



- Superimposable dose-dependent profiles
- All point estimates close to 100% with confidence intervals well within margins
- Equivalent responses in both PD markers relevant for all approved indications

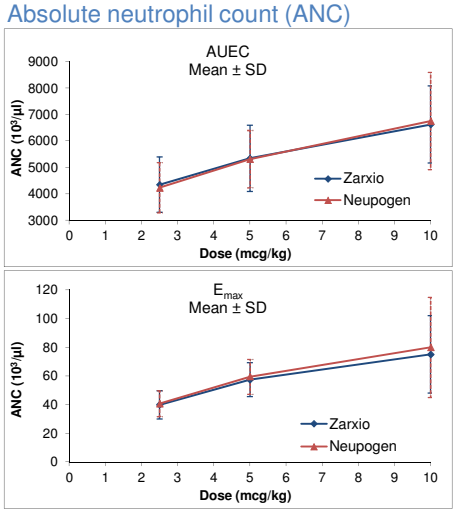
CD34+ profiles in Healthy Volunteers



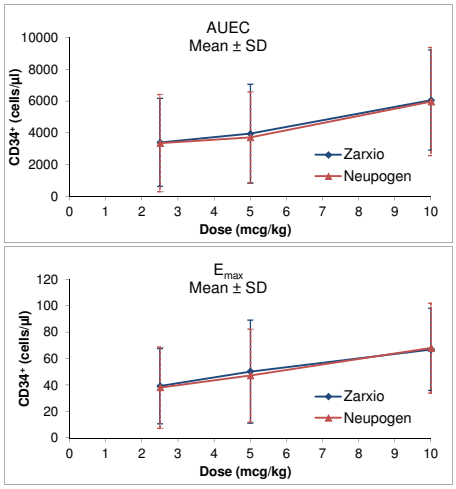
46

Similar Dose-Response Relationships Multiple-Dose Studies (2.5/5/10 mcg/kg s.c.)

Absolute neutrophil count (ANC)



CD34+ cell count



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Study 302
(NCT01519700)

Final Confirmation of Similarity in Breast Cancer Patients Treated with Myelosuppressive Chemotherapy

Study 302 - Breast Cancer as a Sensitive Setting to Confirm Biosimilarity

Breast cancer, TAC chemotherapy, primary endpoint:

- Homogenous population
- Treatment guidelines support use of TAC chemotherapy as a standard curative treatment in early breast cancer patients
- TAC chemotherapy has a proven dose-limiting hematological toxicity with grade 3-4 neutropenia in approx. 65.5% patients and a median duration of grade 4 neutropenia of 7 days without G-CSF support
- Treatment guidelines require primary prophylaxis with G-CSF as supportive care for TAC chemotherapy with a proven substantial effect in this setting
- The duration of severe neutropenia has become a well-established, objective measure of efficacy (risk of infection is directly proportional to severity and duration of neutropenia)
- Well-established model to study and compare products in the G-CSF class

➢ **All study design aspects were pre-discussed with FDA**

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Study 302 - Study Objectives

Primary objective:

- Assess non-inferiority in the mean duration of severe neutropenia (DSN) during Cycle 1 in breast cancer patients receiving TAC chemotherapy

  DSN is defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 10^9/L)

Secondary efficacy endpoints:

- Incidence of febrile neutropenia (FN), defined as oral temperature ≥ 38.3°C while having an ANC < 0.5 × 10^9/L, by cycles and across all cycles
- Number of days of fever, defined as orally temperature ≥ 38.3°C, by cycles and across all cycles
- Depth of ANC nadir in Cycle 1
- Time to ANC recovery in Cycle 1
- Frequency of infections by cycle and across all cycles
- Incidence and duration of hospitalization due to FN

Safety endpoints:

- Incidence, occurrence, and severity of (serious) adverse events
- Local tolerability at the injection site
- Systemic tolerance

Objective of special interest:

- Immunogenicity (anti-rhG-CSF antibody formation)

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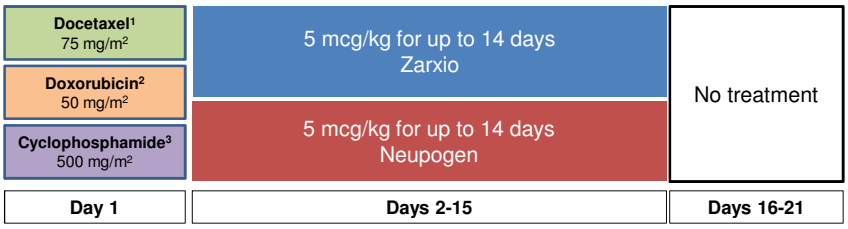
Study 302 – Treatment Regimen per Cycle

- TAC is applied according to the label as approved by FDA
- G-CSF is applied daily starting on Day 2 at a dose of 5 mcg/kg until ANC has recovered to $10x10^9$/L or until Day 15, whichever occurs first

Treatment regimen in each cycle



[1]: Taxotere
[2]: Adriamycin
[3]: Cytoxan

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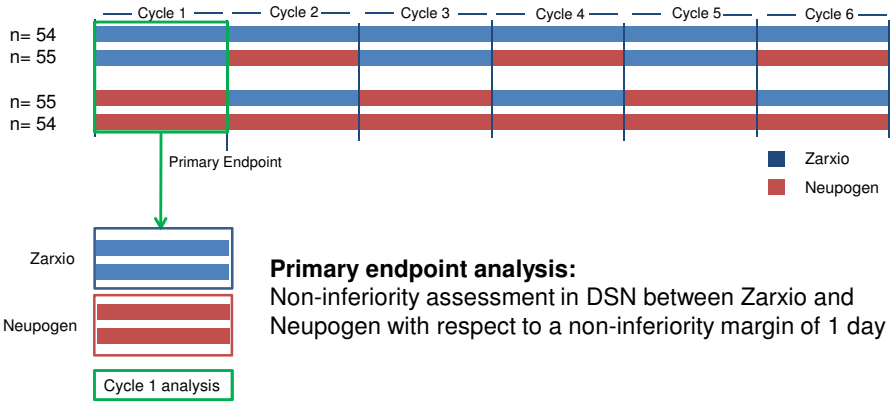
Study 302 – Primary Analysis of Zarxio vs. Neupogen

218 patients were included in 25 sites between 12/2011 and 09/2012



Primary endpoint analysis:
Non-inferiority assessment in DSN between Zarxio and Neupogen with respect to a non-inferiority margin of 1 day

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Study 302 - Baseline Characteristics

For Patients Treated with Zarxio or Neupogen in Cycle 1

Parameter	Zarxio N=107	Neupogen N=107	Total N=214
Age [Mean± SD]	49.5 ±11.52	48.4 ± 11.02	49.0 ± 11.34
Time since initial diagnosis in months [Median (min, max)]	1.0 (0,171*)	1.0 (0,16)	1.0 (0,171*)
Clinical stage n (%)			
I	7 (6.5)	8 (7.5)	15 (7.0)
II	57 (53.3)	53 (49.5)	110 (51.4)
III	43 (40.2)	46 (43.0)	89 (41.6)
IV	0 (0)	0 (0)	0 (0)
Adjuvant chemotherapy n (%)	63 (58.9)	61 (57.0)	124 (57.9)
Neoadjuvant chemotherapy n (%)	44 (41.1)	46 (43.0)	90 (42.1)

*patient 711-32 was enrolled in the study with contralateral breast cancer diagnosed 1 month prior to enrolment; the initial diagnosis was 171 month before randomization.

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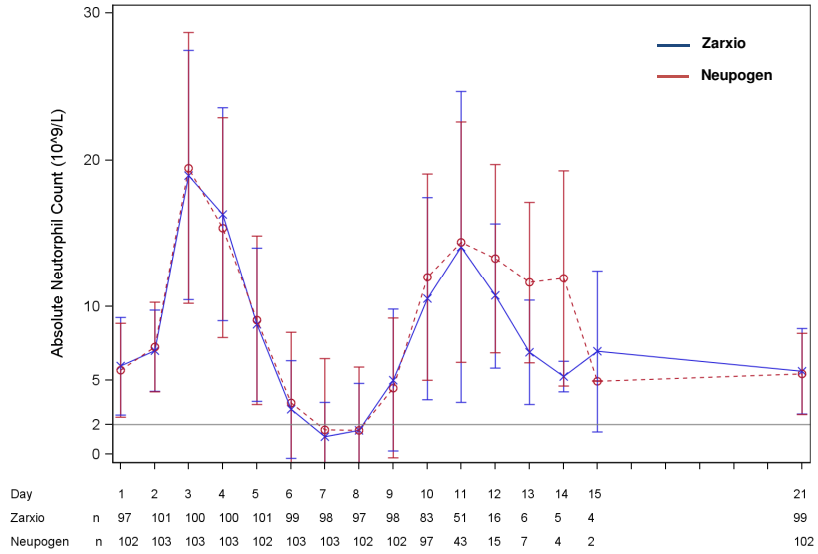
Study 302: Cycle 1 – Superimposable ANC Profiles



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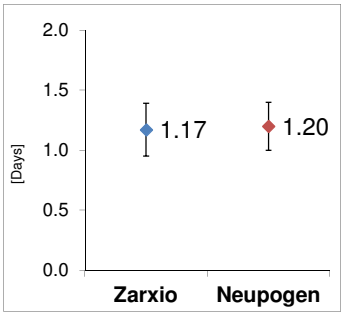
Study 302: Cycle 1 - Primary Endpoint Equivalence in Duration of Severe Neutropenia

Mean DSN on Cycle 1 with 95% CI



Mean (SD) DSN – Cycle 1 [days]

Neupogen – Zarxio	Non-inferiority assessment(1)	Equivalence assessment(2)
0.04	(-0.26; ∞)	(-0.21; 0.28)

(1) One-sided 97.5% confidence interval
(2) Two-sided 90% confidence interval

- ✓ Lower bound of the confidence interval is above the non-inferiority margin of -1 day
- ✓ Non-inferiority between Zarxio and Neupogen established
- ✓ Two-sided confidence interval supports equivalence conclusion

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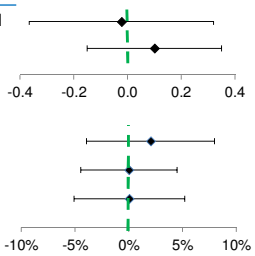
Study 302: Cycle 1 – Similarity in Secondary Efficacy Endpoints

Parameter (Cycle 1)	Zarxio N=101	Neupogen N=103	Comparison Zarxio-Neupogen
Depth of nadir [10^9/L] (mean ± SD)	0.734 ± 1.1388	0.757 ± 1.3131	
Time to ANC recovery [days] (mean ± SD)	1.8 ± 0.97	1.7 ± 0.81	
Incidence of FN (n (%))	4 (4.0%)	2 (1.9%)	
Incidence of hospitalizations due to FN (n (%))	1 (1.0%)	1 (1.0%)	
Incidence of infections (n (%))	2 (2.0%)	2 (1.9%)	
Number of days of fever [days] (median, range)	0 (0 – 2)	0 (0 – 2)	



Definitions:
- **Time to ANC recovery:** number of days until ANC increases to ≥ 2 x 10^9/L after nadir
- **Febrile Neutropenia (FN):** oral temperature ≥ 38.3°C and ANC < 0.5 × 10^9/L on the same day
- **Fever episode:** oral body temperature of ≥ 38.3°C
- **Incidence:** number of patients with at least one such event

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Study 302: Similar Overall Safety Profiles All Six Cycles with Continuous Treatment

Event category	Zarxio N=53 n (%)	Neupogen N=52 n (%)
Any AE	52 (98.1)	50 (96.2)
Study drug-related AEs	19 (35.8)	20 (38.5)
Chemotherapy-related AEs	49 (92.5)	50 (96.2)
Any SAE	5 (9.4)	2 (3.8)
Study drug-related SAEs	0 (0.0)	0 (0.0)
Chemotherapy-related SAEs	3 (5.7)	2 (3.8)

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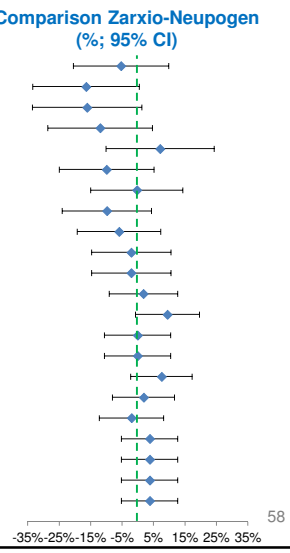
Most Frequent (> 5%) AEs by Preferred Term All Cycles – Continuous Treatment

Preferred term	Zarxio N=53 n (%)	Neupogen N=52 n (%)
Alopecia	41 (77.4)	43 (82.7)
Nausea	29 (54.7)	37 (71.2)
Asthenia	20 (37.7)	28 (53.8)
Bone pain	13 (24.5)	19 (36.5)
Fatigue	17 (32.1)	13 (25.0)
Decreased appetite	8 (15.1)	13 (25.0)
Vomiting	9 (17.0)	9 (17.3)
Anemia	6 (11.3)	11 (21.2)
Diarrhea	5 (9.4)	8 (15.4)
Neutropenia	5 (9.4)	6 (11.5)
Erythema	5 (9.4)	6 (11.5)
Leukopenia	4 (7.5)	3 (5.8)
Pyrexia	6 (11.3)	1 (1.9)
Abdominal pain	3 (5.7)	3 (5.8)
Arthralgia	3 (5.7)	3 (5.8)
Musculoskeletal pain	5 (9.4)	1 (1.9)
Stomatitis	3 (5.7)	2 (3.8)
Myalgia	2 (3.8)	3 (5.8)
Febrile neutropenia	3 (5.7)	1 (1.9)
Dizziness	3 (5.7)	1 (1.9)
Headache	3 (5.7)	1 (1.9)
Peripheral sensory neuropathy	3 (5.7)	1 (1.9)



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Overall Immunogenicity in Breast Cancer Patients and in Healthy Volunteers

No Signs of Induced Immunogenicity in over 3300 Samples Tested

No Signs of Immunogenicity in Breast Cancer Patients and Healthy Volunteers

Breast cancer patients:

Study	Cycles	Dose	Subjects	Samples	RIP positive	NAB positive
302	Up to 6	5 mcg/kg	214	1583	0	n/a
301	Up to 4	300 mcg if < 60kg 480 mcg if ≥ 60kg	170	643	0	n/a
Total			384	2226	0	n/a

Healthy volunteers:

Applications	Dose	Subjects	Samples	RIP positive	NAB positive
Single-dose	1 – 10 mcg/kg	156	486	3*	0
Multiple-dose	2.5 – 10 mcg/kg	208	597	0	n/a
Total		364	1083	3*	0

* All three confirmed positive samples derive from the same subject; subject was already showed a signal at baseline, with no increase in titer after treatment, i.e. likely not driven by a response to G-CSF

RIP: radioimmunoprecipitation assay to assess binding antibodies; NAB: assesses neutralizing antibodies

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Post-marketing Experience with Zarxio

Marketed as Zarzio and as Filgrastim Hexal Outside the US

Summary of Experience Outside US

- Zarzio was first approved by EMA in 2009 and is now approved in over 60 countries worldwide
- Over 7.5 million patient-days of exposure (currently the most prescribed daily filgrastim in Europe)
- Safety is monitored in several post-marketing studies as well as by routine pharmacovigilance
  - To date, more than 3800 patients treated with Zarzio have been observed in post-marketing studies in a wide range of indications covering Chemotherapy Induced Neutropenia, Hematopoietic Stem Cell Mobilization, and Severe Chronic Neutropenia
- No signals of a potential difference in the safety profile as compared to Neupogen
- No cases of immunogenicity reported to date
- No additional risk minimization activities are required beyond those included in the product information

➢ Safety and effectiveness confirmed in clinical practice

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Stem Cell Mobilization Study (501)
Non-interventional Study in Healthy Unrelated Stem Cell Donors

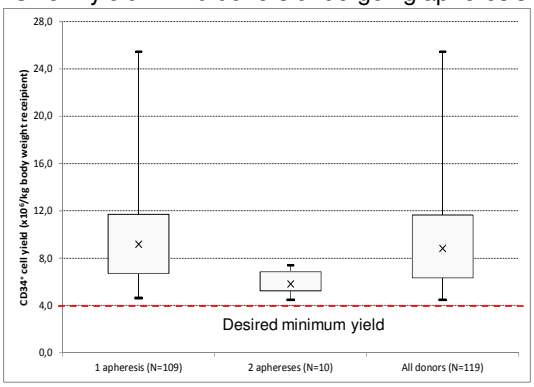
Study objectives:

- Efficacy of stem cell mobilization with Zarzio
- (Long-term) Safety assessment

Treatment:

- s.c. injections of 10 mcg/kg per day
- Apheresis starts at Day 5 of mobilization
- Target of mobilization: harvest of 4 x 10^6 $CD34^+$ cells/kg recipient body weight

$CD34^+$ yield in 119 donors undergoing apheresis*



- $CD34^+$ yield in all donors exceeded minimum target harvest of $4x10^6$ per kg bodyweight of the recipient
- Confirms results seen for $CD34^+$ cell count in healthy volunteer PK/PD studies

*Interim Analysis Based on Data Cut-off Aug 2013

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Overall Conclusions Based on Human Experience with Zarxio

Summary of Human Efficacy and Safety Data

- PK equivalence established in healthy volunteers
- Equivalent ANC response across different treatment regimens in breast cancer patients and in healthy volunteers
- Similar $CD34^+$ cell response in healthy volunteers and proven effectiveness in healthy donors (post-marketing study)
- Similar response profile as compared to Neupogen in all indications evaluated in clinical trials as well as post-marketing outside the US

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Summary of Human Efficacy and Safety Data

- Incidence and nature of AEs were similar for Zarxio and Neupogen in all populations studied
- No signs of immunogenicity
- No concerning or unexpected safety findings for Zarxio throughout entire clinical program as well as through post-marketing surveillance

➢ No clinically meaningful differences between Zarxio and Neupogen

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Agenda

Introduction	**Mark McCamish, MD, PhD** Global Head Biopharm. & Oncology Injectables Development *Sandoz*
Analytical Demonstration of Biosimilarity	**Hansjoerg Toll, PhD** Head Analytical Characterization *Sandoz*
Biosimilar Clinical Development Program	**Sigrid Balser, PhD** Global Clinical Development *Sandoz*
A Clinical Perspective on Biosimilarity	**Louis Weiner, MD** Professor and Director of Lombardi Comprehensive Cancer Center *Georgetown University*
Totality of the Evidence and Concluding Remarks	**Mark McCamish, MD, PhD** Global Head Biopharm. & Oncology Injectables Development *Sandoz*

A Clinical Perspective on Biosimilarity

Louis M. Weiner, MD
Director, Lombardi Comprehensive Cancer Center
Francis L and Charlotte G Gragnani Professor
Chairman, Department of Oncology
Georgetown University Medical Center

Conflicts of Interest

- Sandoz (Consultant)*
- Merrimack Pharmaceuticals (Scientific Advisory Board, Stock Options)
- Celldex Pharmaceuticals (Scientific Advisory Board, Stock Options)
- TDT Therapeutics (Stock)
- Jounce Therapeutics (Scientific Advisory Board, Stock Options)
- AbbVie (Scientific and Clinical Advisory Boards)
- Immunome (Scientific Advisory Board)
- CytoMx (Scientific Advisory Board)

* Relevant to this presentation

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What criteria need to be met for me to treat a patient with this biosimilar?

- ❑ Does the originator molecule have meaningful clinical value?
- ❑ Does the biosimilar have equivalent properties as the originator?
- ❑ Does the biosimilar have efficacy and toxicity profiles that are consistent with those of the originator?
- ❑ Is extrapolation reasonable if biosimilarity is demonstrated?
- ❑ Will use of the biosimilar lower costs?

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Does the originator molecule filgrastim have meaningful clinical value?

- G-CSF has been widely used around the world for more than 20 years
- Indications in the US include:
  - Cancer patients receiving myelosuppressive chemotherapy
  - Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
  - Cancer patients receiving bone marrow transplant
  - Patients undergoing peripheral blood progenitor cell collection and therapy
  - Patients with severe chronic neutropenia

Unquestioned clinical value helps patients

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G-CSF is Underused and Badly Used

Choi MR et al. Support Care Cancer 2014; 22:1619-28

Design:

- US Medicare database used to link 12,707 courses of chemotherapy for 5 common cancers to G-CSF use in patients receiving high-risk chemotherapy regimens

Results:

- G-CSF given to less than 50% of eligible patients receiving a high-risk chemotherapy regimen
- Depending upon tumor type, 4.8-22.6% of patients receiving a high-risk regimen experienced chemotherapy-induced neutropenic complication (CINC) requiring hospitalization

Kreys ED, et al. J Oncol Practice; 2014; 10:168-73

- G-CSF compliance reduces emergency room admission rate from 25.9% to 10.5% (OR 0.34; $p<0.001$) and patient care cost savings

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Proper Use of G-CSF Benefits Patients and Reduces Costs

Weycker, et al. BMC Health Services Research 2014; 14:189

Design:

- Retrospective cohort design using US healthcare claims data from 2001-2010 – 135,921 patients, 5,577 received daily filgrastim
- Included all patients who initiated ≥ 1 course myelosuppressive chemo and received daily filgrastim ≥ 1 cycle
- Followed for CINC, mortality, costs

Results:

Days of Filgrastim (n)	CINC Risk	Mortality (%)	Mean Expenditures ($)
1-3 (8,371)	2.4	8.4	18,912
4-6 (3,691)	1.9	4.0	14,907
≥7 (2,226)	1.0	0	13,165

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Does the biosimilar have equivalent properties as the originator?

- Identical properties not necessary
  - Structure, function and bioactivity are all identical or similar to originator G-CSF
- At most, minor differences in formulation
  - e.g., glutamate as opposed to acetate buffer

The preponderant evidence supports biosimilarity

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Do Neupogen and Zarxio have similar efficacy and toxicity profiles?

- Proof of biosimilarity does not require comprehensive clinical testing per FDA, but thorough analysis of the available clinical data is essential
  - Clinical trial results possess more intrinsic variability than detailed molecular analysis when analyzing biosimilarity
    - e.g., patient selection, study size, trial design

Analysis of the clinical trial results supports the similarity of originator and biosimilar efficacy and toxicity profiles

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Do Neupogen and Zarxio have similar efficacy and toxicity profiles?

- Vast world-wide experience with Zarzio
  - 7.5 million treatment days analyzed since 2009 across many indications
  - Not rigorously collected data from randomized, controlled clinical trials, BUT
  - Large body of relevant information of interest
  - No obvious signs of unexpected toxicities or inefficacy

Comforting context for a prescribing physician

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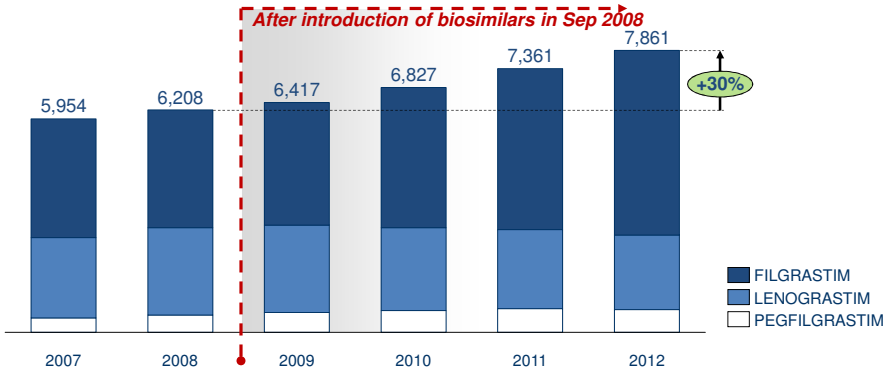
The Introduction of Filgrastim Biosimilars Coincided with More G-CSF Use in Europe

Total G-CSF market volume in Europe by year
Number of syringes in thousands

Note: Data covers full year sales. Source: IMS



- Reduced drug costs and improved adherence to guidelines in Southern Sweden (Gascon P, et al. Support Care Cancer 2013; 21:2925-32)

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Is extrapolation reasonable if biosimilarity is demonstrated?

- Paradigm shift of biosimilars – "where the rubber meets the road"
- If the molecule is biosimilar then it stands to reason that extrapolation to the originator's indications is warranted
  - Additional safety and efficacy context provided by Zarzio worldwide experience adds confidence

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Will the use of biosimilar lower costs?

- Introduction of the biosimilar will lower drug costs and spur competition
- Data from Europe suggest that introduction of biosimilars has:
  - Increased utilization of guidelines
  - Improved clinical outcomes
  - Reduction of drug costs

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What criteria need to be met for me to treat a patient with this biosimilar?

- ☑ The originator molecule has meaningful clinical value
- ☑ The biosimilar possesses equivalent properties as the originator
- ☑ The biosimilar's efficacy and toxicity profiles are consistent with those of the originator
- ☑ Extrapolation is reasonable if FDA agrees that biosimilarity has been demonstrated
- ☑ Use of the biosimilar is likely to lower costs

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Totality of the Evidence and Concluding Remarks

Mark McCamish, MD, PhD
Global Head Biopharm. & Oncology Injectables Development
Sandoz

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Findings from the Analytical Program

- Zarxio is highly similar to Neupogen
  - Identical primary structure
  - Highly similar secondary and tertiary structure
  - Highly similar purity and stability profiles
  - Highly similar receptor binding and biological activity

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Summary of Clinical Evidence

- Efficacy data confirm similarity
  - PK/PD with ANC and $CD34^+$ cells confirm similarity
  - DSN in the range of what is reported for Neupogen in this setting
  - Tight confidence interval with lower boundary of approx. ¼ day
  - Data would also support equivalence within tight limits (-0.21; 0.28)
  - Extrapolation justified by totality of data

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Summary of Safety Data

- Incidence and nature of AEs were similar for Zarxio and Neupogen
  - In cancer patients receiving myelosuppressive chemotherapy (Study 302)
  - In healthy volunteers (PK/PD Studies)
- No concerning or unexpected safety findings for Zarxio throughout entire clinical program
  - Repeated switching did not an negative impact on safety profiles
- Incidence and nature of AEs similar throughout post-marketing experience

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Summary

- Biologic drugs are important therapeutic agents that are very costly and access may be limited
- Modern technology and analytics allow full characterization and creation of biosimilars
- Zarxio has been demonstrated both analytically and clinically to be highly similar to the reference product, Neupogen
- This high similarity justifies extrapolation to all indications for the reference product
- Approval of Zarxio will expand options available to healthcare providers and patients

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Zarxio™ (filgrastim)

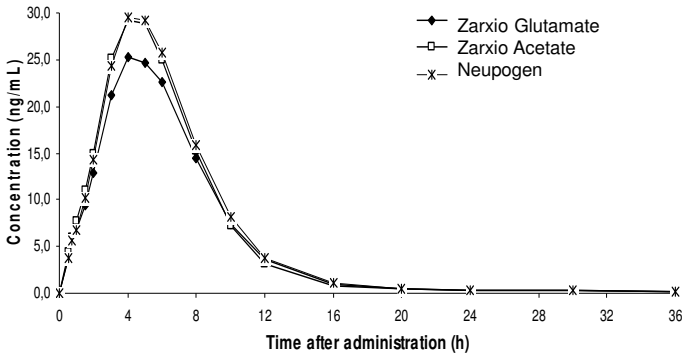
Sandoz, a Novartis Company

Presentation to the Oncologic Drugs Advisory Committee

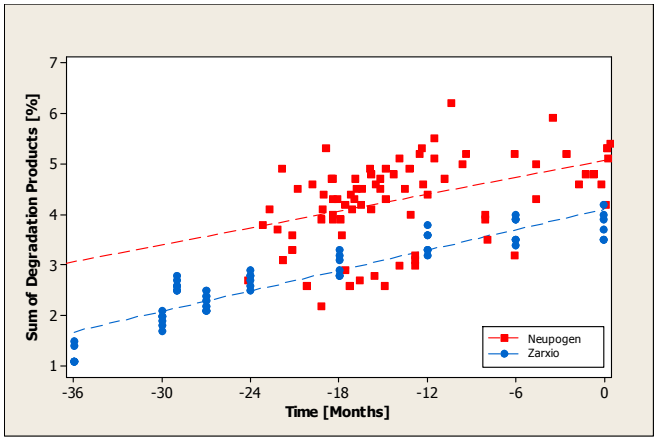
January 7, 2015

Backup Slides

Figure 22
Arithmetic Mean of Serum Concentrations of ZARXIO Glutamate, ZARXIO Acetate, and Neupogen
PP Population, n = 28



Intended Storage Condition (2-8 ℃)



Rate of degradation:
Zarxio: 0.07 %/month
Neupogen: 0.06 %/month

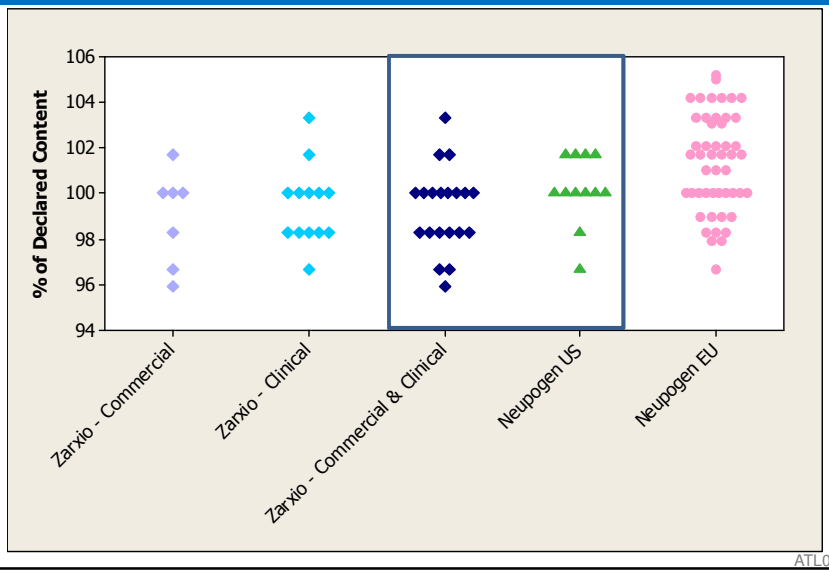
ATL049 - 90

Regulatory History and FDA Communications (1/2)

- **October 1st 2009: PDUFA Type B PreIND meeting**
  - Discussed the development program of Zarxio under 351(a) pathway
- **March 23rd 2010: Biosimilar 351(k) pathway** was established under BPCI Act
- **October 11th 2010: PreIND meeting**
  - Determined the path forward for the development of Zarxio using the biosimilar 351(k) pathway
- **November 1st 2010: Submitted study designs** of pivotal Study 302 and Study 109 for FDA's feedback
- **April 4th 2011: Received FDA's feedback on the study designs**

REG006 - 91

Zarxio can be Manufactured to Match Neupogen in Content



ATL098 - 92

Autologous Stem Cell Transplant in Pediatric Patients – Physician Led Report

- A retrospective study on cases treated at three Italian pediatric transplant centers, from January 2011 to October 2013
- Data were collected on 29 children (mean age 4.6 years) with solid tumor or non-Hodgkin's lymphoma undergoing first peripheral blood stem cell (PBSC) mobilization with Zarzio and chemotherapy and compared with a case-matched historical control group (n=29)
- No major and/or unexpected side effects were reported; mild bone pain and headache each in one patient
- Peak peripheral blood CD34+ cell count of 20 × 106/L was achieved in 90% of patients, with a median value of 71 × 106/L; 83% of patients reached the desired target (CD34+/kg) dose.
- No differences were observed in comparison with historical control group mobilized with originator filgrastim.

Cesaro S, et al. *Transfusion*. 2014 Jul 29. doi: 10.1111/trf.12789.